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Estimating Human Equivalent No Observed Adverse Effect Levels for VOCs (Volatile Organic Compounds) Based on Minimal Knowledge of Physiological Parameters

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J.H. Overton and A.M. Jarabek	

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16. ABSTRACT

The U.S. EPA advocates the assessment of health effects data and calculation of "inhaled reference doses" as benchmark values for gauging systemic toxicity to inhaled gases. This assessment often requires an inter- or intra-species dose extrapolation from "no observed adverse effect level" (NOAEL) exposure concentrations in animals to human equivalent NOAEL exposure concentrations. To achieve this, we have developed a dosimetric extrapolation procedure based on the form or type of equations that describe the uptake and disposition of inhaled volatile organic compounds (VOCs) in physiologically-based pharmacokinetic (PB-PK) models. The procedure assumes allometric scaling of most physiological parameters and that the value of the time integrated human arterial blood concentration must be limited to no more than to that of experimental animals. The scaling assumption replaces the need for most parameter values and allows the derivation of a simple formula for dose extrapolation of VOCs that gives equivalent or more conservative exposure concentrations values than those that would be obtained using a PB-PK model in which scaling was assumed.

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ESTIMATING HUMAN EQUIVALENT NO OBSERVED ADVERSE EFFECT LEVELS FOR VOCs BASED ON MINIMAL KNOWLEDGE OF PHYSIOLOGICAL PARAMETERS

John H. Overton

Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711, USA.

Annie M. Jarabek

Environmental Criteria and Assessment Office
and
Health Effects Research Laboratory
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711, USA.

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INTRODUCTION

The U.S. Environmental Protection Agency (U.S. EPA) advocates the assessment of health effects data and calculation of "inhaled reference doses" (RfD_i) for the health risk assessment of the noncancer effects of inhaled hazardous agents. An inhalation reference dose (RfD_i) is an estimate of a continuous inhalation exposure over a human lifetime that is unlikely to pose significant risk of adverse noncancer health effects and serves as a benchmark value for assisting in risk management decisions (U.S. EPA, 1989)[2]. Derivation of an RfD_i involves dose-response assessment of diverse animal data to determine the exposure levels at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control. This assessment often requires an interspecies dose extrapolation from a "no observed adverse effect level" (NOAEL) exposure concentration of an animal ($NOAEL_A$) to a human equivalent NOAEL ($NOAEL_{HEC}$) that would or is assumed to result in a human dose being no more than the similarly defined dose measured or estimated for the experimental animal. The RfD_i is operationally derived from the $NOAEL_{HEC}$ by the application of generally order-of-magnitude uncertainty factors (UFs) which reflect potential extrapolation uncertainties (U.S. EPA, 1989)[2].

The RfD_i requires extrapolation of concentrations from intermittent exposure scenarios in animals (e.g., 6 hours/day, 5 days/week) to chronic continuous human exposure conditions (U.S. EPA, 1989)[2]. Relationships between external exposures and internal concentrations depend upon complex simultaneous and consecutive processes of absorption, distribution, metabolism, storage, detoxification and elimination. Physiologically-based pharmacokinetic (PB-PK) models which account for some these complex processes have proven to be useful tools for estimating delivered doses and internal concentrations. The models require that the values of physiological parameters be sufficiently detailed to describe species differences in absorption and metabolism. Since these data are not available for most compounds, an approach is needed for those situations in which an extensive knowledge of parameter values is lacking.

In order to be able to estimate $NOAEL_{HEC}$s in those cases for which the use of PB-PK models is not possible due to data gaps, we have developed a dosimetric extrapolation procedure based in part on the form or type of equations associated with PB-PK models. With the exception of partition coefficients and Michaelis constants, this proposed method assumes that physiological or model parameters can be extrapolated from one species to another by allometric scaling and that the relevant dose for basing dose extrapolations is the time integrated or the average arterial blood concentration of the inhaled gas. The assumptions "replace" the need for most parameter values and allow the derivation of a simple formula for dose extrapolation that gives equivalent or more conservative exposure concentrations values than those that would be obtained, in principle, with a PB-PK model used in conjunction with the same assumptions.

METHODS

Assumptions

Assumptions imposed by the RfD_i methodology (U.S. EPA, 1989)[2]:

Assumption 1. Non-cancer toxic effects observed in chronic bio-assays are the basis for the determination of $NOAEL_A$s and the derivation of RfD_i for human exposures. "Lifetime" chronic animal exposure scenarios are deemed equivalent to humans lifetime (70 years) exposures.

Assumption 2. Human exposure is continuous and constant for 70 years. The animal exposure scenario is experiment dependent; however it is usually intermittent and periodic (e.g., 6 hours/day, 5 days/week, repeated for many weeks).

Additional assumptions for the proposed method:

Assumption 3. The animal exposure scenario is periodic and all concentrations of the inhaled compound within the animal are periodic with respect to time. The internal human concentrations are in dynamic equilibrium and constant with respect to time. Practically, these conditions should be met during "most" of the time. For example, if this condition is met for nine tenths of the time (e.g., periodic during the last 90 weeks of a 100 week experiment), then estimates of average concentrations will be in error by less than 10%.

Assumption 4. $NOAEL_{HEC}$s are defined in terms of the requirement that the concentration of the inhaled compound in the arterial blood (leaving the lung) of the human be no greater than the average of the arterial blood concentration leaving the lung of the laboratory species. This is equivalent to requiring that the time integrated arterial blood concentration of the inhaled gas (CAxT) of the human be less than that of the animal for the same time length.

Because the specification of a biologically effective toxic dose to a given target tissue is not possible, the definition of a surrogate dose must be somewhat arbitrary. However, the toxic effects of some compounds are expected to be directly related to the inhaled parent compound; furthermore, CAxT is an internal dose and is "closer" to being the the target dose than is the exposure concentration. Basing the effective dose extrapolation on another surrogate (e.g., metabolite) would require knowledge of the interspecies metabolism for the compound of interest and additional information about human and animal physiological parameters.

Assumption 5. In principle, PB-PK models could or do accurately describe the uptake, distribution, and fate of inhaled volatile organic compounds (VOC).

Assumption 6. For the two species for which a dose extrapolation is being made all physiological parameters, except for the partition coefficients and the Michaelis constant, scale in an allometric manner. That is, kinetic parameters are proportional to body weights to some power. Specifically: volumes scale in proportion to body weight; perfusion rates, ventilation, and

each Vmax for all saturable paths (e.g., metabolism) scale in proportion to body weight to some power, p; rate constants for first order processes (e.g., chemical reactions, elimination, clearance, non-saturable metabolism) scale in proportion to body weight to the power p-1; the Michaelis constant, Km, is the same in humans and laboratory animals.

Derivation of Proposed Extrapolation Formula

The dynamics of the uptake and disposition of inhaled gases are described in terms of a set of first order differential equations. Each equation describes the dynamics of the concentration of the inhaled compound in a compartment due to loses and gains by perfusion as well as to linear and saturable processes. The parent compound is completely mixed within a compartment and a compartment may represent a part or all of a tissue type or organ. In compartments composed of both blood and tissue, equilibration between blood and tissue is assumed.

Schematics of the types of compartments considered are given in Figure 1. The general non-respiratory tract compartment, which can be in parallel or in series with other similar compartments, is displayed in Figure 1A. There are several sources of input and exit of the inhaled compound by perfusion (although the latter is represented only by one) and as many pathways of losses as necessary, such as elimination and metabolism. These pathways are linear or, if saturable, of the Michaelis-Menten type. In keeping with most PB-PK models, we assume that the RT compartment (Figure 1B) is well mixed in which the trace gas in the RT air is in equilibrium with that in the RT blood.

The reader is refered to the appendix for the mathematical details of the derivation, the consequences of which are given in the next section.

RESULTS

General Consequences of the Proposed Method

1) The determination of $NOAEL_{HEC}$s is as follows: if the ratio of the blood to air partition coefficients of the animal and human is greater than one, then $NOAEL_{HEC}$ = the time averaged animal exposure concentration (the animal's "adjusted" NOAEL, $NOAEL_{[ADJ]}$); if the ratio is less than one, then $NOAEL_{HEC}$ = $NOAEL_{(ADJ)}$ multiplied by the ratio.

2) Relative to PB-PK model (in which the parameters satisfy the assumptions of the proposed method) results, the proposed $NOAEL_{HEC}$s are conservative; i.e., they are less than or equal to those predicted by the PB-PK model.

3) The blood concentration of the inhaled compound in any human compartment is less than the average concentration in the blood of the corresponding animal's compartment.

4) The rate of metabolite production per cardiac output or per tissue perfusion rate in humans does not exceed the average of that in the animal species.

In order to obtain a perspective as to the significance of the proposed method, it's predictions of $NOAEL_{HEC}$s for methylene chloride (dichloromethane, DCM) are compared to predictions of three other possible methods. The three methods are identified as "optimal", "similar", and "established".

In the first two methods, a PB-PK model was used for dose extrapolation. The optimal method used the model in conjunction with an extensive set of experimentally determined physiological parameters, those of Andersen et al.(1987)[3]. The same model and human parameters were used in the similar approach; however, the animal parameters were determined by scaling from the human values as defined by Assumption (6) of the proposed method. This method conforms to the assumptions of the proposed method. The established method was recommended by the U.S.EPA (1980)[1] for drinking water and has been applied to inhalation. This dosimetric extrapolation procedure involves calculating $NOAEL_{HEC}$s by multiplying $NOAEL_{(ADJ)}$s by the ratio of ventilation rate divided by body weight of the animal to ventilation rate divided by body weight of the human.

The PB-PK simulations were carried out for three species, human, rat and mouse. For the animal exposure scenario, 6 hours per day, 5 days per week was chosen. Simulations at different exposure levels generated arterial blood concentrations for humans and average values for the laboratory animals. The plots of $NOAEL_{HEC}$ versus $NOAEL_A$, displayed in Figure 2 along with those of the proposed and established methods, were created by choosing the equivalent exposure concentrations that resulted in the human arterial blood concentration being equal to the average of the laboratory animal's.

In keeping with the results of the derivation, the proposed $NOAEL_{HEC}$s are less than the similar method results (i.e., using a PB-PK model subject to the proposed method assumptions).

With respect to the relationship of the proposed predictions to the other methods of calculation, the following observations are noted. The proposed method plots are parallel to the established method plots and result in 3.4 and 6.9 times smaller or more conservative $NOAEL_{HEC}$s estimates for the rat and mouse, respectively. The proposed rat $NOAEL_{HEC}$s also fall below those of the optimal method by factors ranging from 1.4 to 2.4. Except at higher exposure concentrations (above approximately 1600 mg/m3, 466 ppm), where it is smaller by a factor of about 1.3, the proposed mouse $NOAEL_{HEC}$s are as much as 1.5 times as large as the optimal mouse $NOAEL_{HEC}$s. Obviously, the mouse, as defined by the optimal model parameters, is not similar to humans.

The established method results in the largest and most liberal $NOAEL_{HEC}$s of the four methods. The $NOAEL_{HEC}$s of the established method lie above those of the optimal method results by factors that range from 1.6 to 2.6 for the rat and 8 to 9.8 for the mouse. For the rat, the similar $NOAEL_{HEC}$s are nearly the same as those of the optimal method. For the mouse, the similar $NOAEL_{HEC}$s lie above those of the optimal method. This means that the similar method would result in a less conservative $NOAEL_{HEC}$ than the optimal method when extrapolating from toxicity data in mice.

It should be noted that the mouse is a more conservative predictor of $NOAEL_{HEC}$ than the rat for the optimal, similar, and proposed methods; however, the mouse would result in a more liberal $NOAEL_{HEC}$ estimate relative to extrapolation from rat data using the established methodology. This "flip-flop" is a property of the established method in which the ratio of the animal ventilation rate divided by the animal body weight to the human ventilation rate divided by the human body weight is multiplied by the $NOAEL_{(ADJ)}$ to obtain the $NOAEL_{HEC}$; generally, this ratio increases with decreasing body weight.

DISCUSSION

Accurate extrapolation of animal toxicity data for human health risk assessment requires determination of the effective dose to the target tissue and the sensitivity of the target tissue to that dose. These issues need to be addressed when attempting to put into perspective the results of the proposed method as well as the other extrapolation methods presented. The $NOAEL_{HEC}$s (Figure 2) computed by the four methods represent values to which uncertainty factors (UFs) would be applied to operationally derive RfD_is. Generally, a 10-fold factor is applied to reflect uncertainties in interspecies (animal to human) extrapolation; i.e., to account for uncertainties in dose extrapolation and sensitivity differences. A 10-fold factor applied to the established methodology would result in a RfD_i slightly below but in more agreement with the $NOAEL_{HEC}$s of the optimal, similar, and proposed methods. Note that the optimal method, which takes into account an extensive set of experimentally determined physiological parameters for estimating internal concentrations (and presumedly the most accurate method of extrapolation), is considerably more conservative than the established method in its resulting estimate. The application of an UF of 10 that has been used to account for both dose and sensitivity uncertainties to results of model based dose extrapolation methods may be inappropriate since the dosimetry has accounted for some interspecies variability.

The fact that the proposed method is more liberal than the optimal method for the mouse for $NOAEL_A$s less than 1600 mg/m_3 illustrates a possible result of non-similarity. Nevertheless, if we consider the optimal results as representing the best possible dose extrapolation based on internal blood concentrations, then the proposed results are more realistic than those of the established method. Also, it should be noted that the mouse appears to be more sensitive (i.e., has lower NOAEL levels) than the rat for the optimal, similar and proposed methods, whereas using the established method for both animals the mouse is more liberal than the rat.

Because blood to air partition coefficients are more readily available than is a set of physiological parameters, the proposed method represents a simple alternative approach when PB-PK modeling is not feasible. In some cases a knowledge of the values of the blood to air partition coefficients is not necessary; if it is known only that the ratio of the coefficients is greater than one then a $NOAEL_{HEC}$ can be computed given a $NOAEL_A$. In any case, based on available values, we can expect the ratio not to be far from one. With only a few exceptions and representing several classes of chemical

compounds, for example, the ratio of the coefficients for rat to human for about 50 compounds ranges from 1.5 to 2 (Gargas et al.,1988)[4].

Analyses such as discussed here are useful in examining methods and approaches to extrapolation between species of equivalent doses. This examining process is iterative; improvements can be made as more information and a better understanding of relevant toxicological doses becomes available.

APPENDIX

Derivation of Extrapolation Formula

The time rate change of the mass in the non-RT compartment (Figure 1B) is expressed as,

(1) $dM/dt = \sum_j Q_j*C_j - Q*C - r(C)$;

where,

(2) $r(C) = -[V*(\sum_j k_j)*C + \sum_j Vmax_j*C/(Km_j + C)]$.

In these equations, M is the mass of the compound in the compartment and t is time. C_j is the concentrations in the blood entering the compartment with corresponding perfusion rates, Q_j. The concentration in the blood in the compartment is C and the exiting perfusion rate is Q ($Q = \Sigma Q_j$). Linear and saturable rates are represented by r(C) in Eq. (1). In Eq. (2), V is the compartment volume, the k_j,s are the first order rate constants for the linear processes; $Vmax_j$ and Km_j are the Vmax and Michaelis constant, respectively, for the j-th saturable process.

Because the concentrations and masses within an animal compartment are periodic (assumption 3) the integral of the left hand side of Eq (1) over a time period of the length of the period is zero; thus,

(3) $0 = \sum_j q_j*\bar{C}_j - \bar{C} - \bar{R}$;

where,

(4) $\bar{R} = Vk*\bar{C} + \sum_j v_j*[\overline{C/(Km_j + C)}]$.

and,

(5a) $Vk = \sum_j V*k_j/Q$; for each index, j : $q_j = Q_j/Q$; $v_j = Vmax_j/Q$.

The overbar indicates an averaged term. The factors defined in Eqs (5) are formed by dividing both sides of Eqs (1) and (2) by Q. They are species independent because of the similarity assumption (Assumption 6). Thus, for the same concentration, C, R(C) is species independent; i.e.,

(5b) $R_A(C) = R_H(C)$,

where the left hand and right hand terms are the animal and human scaled rates, respectively.

For humans, the left hand side of Eq (1) is zero at all times as a consequence of the equilibrium assumption for humans (Assumption 3). Thus, Eqs (3) and (4) apply to both animals and human, depending on whether there are overbarred terms (animals) or no overbarred terms (humans).

We now consider the situation in which the concentration in the blood entering a human compartment is no greater than that entering the corresponding compartment of an animal. That is,

(6) $C_j \leq \bar{C}_j$, for each j.

The overbarred terms indicate animal and no overbar indicates human.

A property of the nonlinear convex function of concentration, R(C), is that its average is less than the function evaluated at the average value of C; i.e.,

(7) $\bar{R} \leq R(\bar{C})$.

CONSEQUENCE I. Applying Eqs (6) and (7) to Eq (3) for both humans and animals, one finds that the concentration of the inhaled compound in the blood that is in and is exiting the human compartment is no more than that in the animal compartment; i.e.,

(8) $C \leq \bar{C}$.

CONSEQUENCE II. These results (Eqs (6), (7), and (8)) about an arbitrary compartment allow the following inference: If the human arterial blood concentration of the inhaled compound on exiting the lung is no more than the corresponding average concentration of the animal, then the concentration in human blood in or exiting any non-respiratory tract body compartment is no greater than the average of that in or exiting the corresponding compartment of the animal.

Using Assumptions 1 and 4, the next step is to determine what human exposure will result in the human arterial blood concentrations being no more than the average of the animals'. To do this we must consider the respiratory tract (RT) which is the interface between the atmosphere and the arterial blood.

For the RT (see Figure 1B), we proceed in the same manner as for the body compartment by averaging the equation for the time rate change of mass in the RT compartment. After rearranging,

(9) $QV*\overline{CE} + QC*\overline{CV} = (QV/\lambda + QC)*\overline{CA} + \bar{r}_p$;

where QV is the ventilation rate; QC is the cardiac output; $\bar{r}_p$ is the average loss due to saturable and linear processes, $r_p(CA)$, in the RT; $r_p(CA)$ is of the same form as r(C) in Eq 2. $\overline{CE}$, $\overline{CV}$, and $\overline{CA}$ are the average exposure, venous blood, and arterial or pulmonary blood concentrations, respectively. The blood to air partition coefficient is λ . With the overbar removed Eq. (9) is valid for humans. Both sides of the equation are divided by QV and rearranged, resulting in

(10) $u*\overline{CA} = \overline{CE} + w*\overline{CV} - \bar{R}_p$,

where,

(11) $\bar{R}_p = \bar{r}_p/QV$; $w = QC/QV$; $u = (\lambda^{-1} + w)$.

The first two terms are species independent (Assumption 6); however, u is not because of the species dependent partition coefficient, λ . Using Eq. (10) and the subscripts A and H to indicate animal and human, respectively,

(12) $u_A*\overline{CA} = \overline{CE} + w*\overline{CV} - \bar{R}_{pA}$.

(13) $u_H*CA = CE + w*CV - R_{pH}(CA)$;

Based on the assumptions and conclusions reached so far, it is possible to prove (which is beyond the scope of this presentation) for the human that both CV and CA increase or decrease if CE increases or decreases, respectively. Thus, it is only necessary to determine the $NOAEL_{HEC}$ for that case in which CA = $\overline{CA}$, because if the human exposure concentration is less than that $NOAEL_{HEC}$, then CA < $\overline{CA}$ in keeping with Assumption 4.

Setting CA = $\overline{CA}$ in Eq (13), noting that $\bar{R}_{pA} \leq R_{pA}(\overline{CA})$, that $R_{pH}(\overline{CA}) = R_{pA}(\overline{CA})$ by similarity, and subtracting Eq (13) from Eq (12), we obtain with some rearranging and using the definition of u in Eq (10),

(14) $CE \geq \overline{CE} + w*(\overline{CV} - CV) + (\lambda_H^{-1} - \lambda_A^{-1})*\overline{CA}$.

We infer from CONSEQUENCE II that $\overline{CV} > CV$; thus, the second term on the right side of Eq (14) is positive and may be dropped without changing the direction of the inequality. If $\lambda_H \leq \lambda_A$ then the last term on the right is also positive and may be omitted without affecting the inequality. On the other hand if $\lambda_H > \lambda_A$, then the fact that $\overline{CA} \leq \lambda_A * \overline{CE}$ is used to obtain a second relationship.

For $\lambda_H \leq \lambda_A$:

(15) $CE \geq \overline{CE}$.

For $\lambda_H > \lambda_A$:

(16) $CE > (\lambda_A / \lambda_H)*\overline{CE}$.

The time average of the animal exposure concentration, $\overline{CE}$, is equivalent to the animal's $NOAEL_A$ adjusted for the duration of its exposure time ($NOAEL_{[ADJ]}$; U.S. EPA, 1989[2]). Obviously, choosing the $NOAEL_{HEC}$ to equal the right hand side of Eqs (15) or (16) results in a conservative or exact $NOAEL_{HEC}$ with respect to an extrapolation made with a PB-PK model subject to the assumptions of the proposed method.

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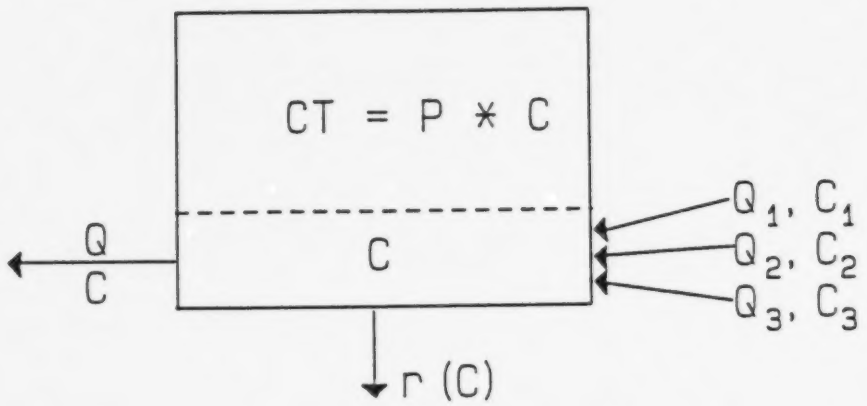
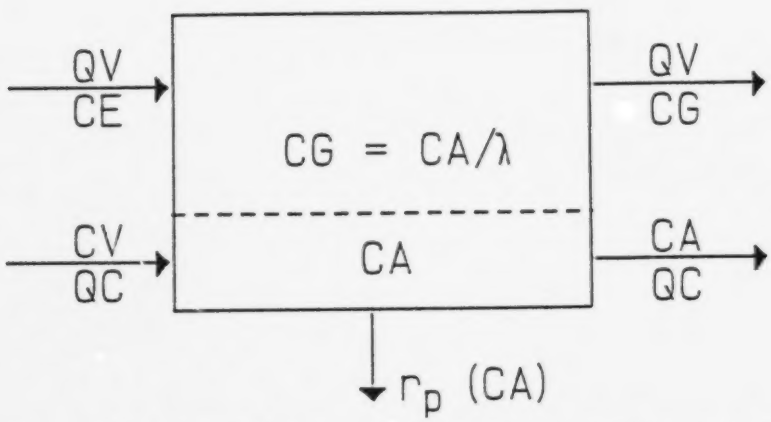


A. Schematic of Generalized Non-Respiratory Tract Compartment



B. Schematic of Respiratory Tract Compartment

Figure 1. A: Schematic of generalized non-respiratory tract compartment. Q_1, Q_2, and Q_3 = entrance perfusion rates from several sources; Q, exit perfusion rate, = $Q_1 + Q_2 + Q_3$; C = concentration of inhaled compound in the blood in or leaving the compartment; C_1, C_2, and C_3 = concentrations in incoming blood; CT = concentration in tissue; r(C) = loses due to linear and saturable processes; P = tissue to blood partition coefficient.

B: Schematic of respiratory tract compartment. QV = ventilation rate; QC = cardiac output; CV = concentration of inhaled compound in the venous blood; CA = concentration in arterial blood; CE = exposure concentration; CG = gas phase concentration in the respiratory tract; $r_p(C)$ = loses due to linear and saturable processes; λ = blood to air partition coefficient.

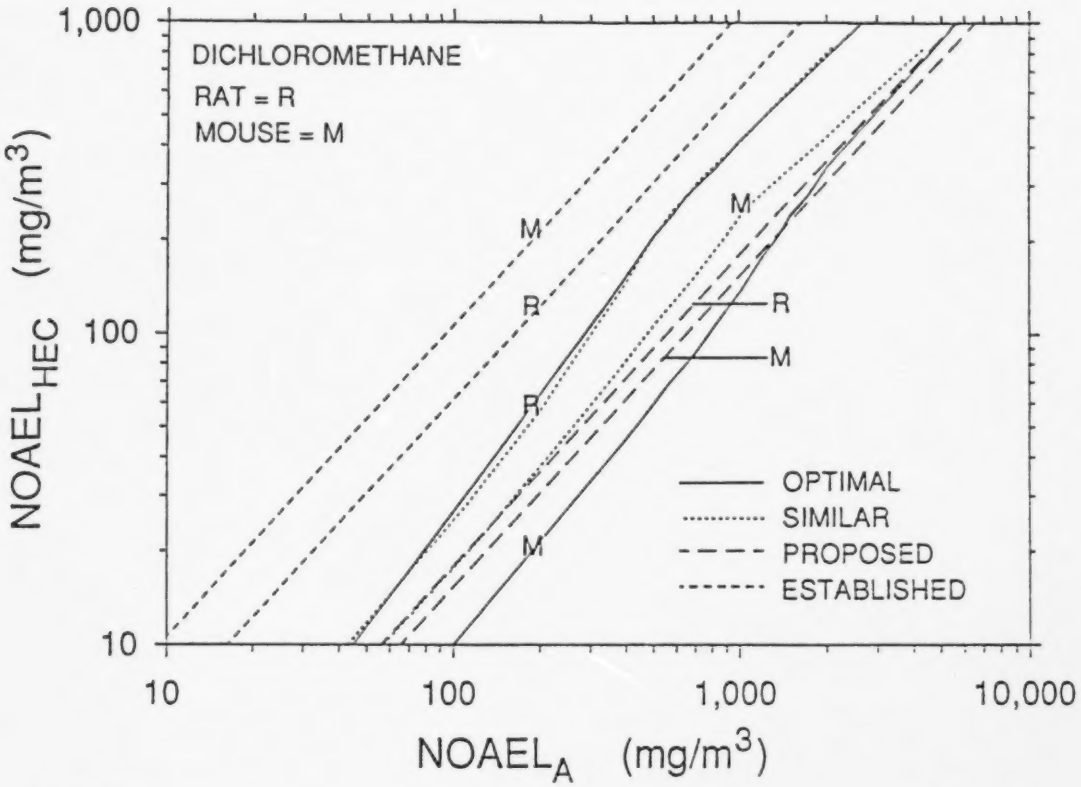


Figure 2. Plotted are values of $NOAEL_{HEC}$ versus $NOAEL_A$ for two animals and four possible methods of determining the $NOAEL_{HEC}$s. The inhaled compound is dichloromethane; animals are rat and mouse, and the methods are indicated by OPTIMAL, SIMILAR, PROPOSED, and ESTABLISHED. The PROPOSED method is described in this paper. (Figure from Overton and Jarabek, 1989)[7].